

10 20 30 40 50 60
 GTTGTGCTG TGGCTGATAG CCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG
 70 80 90 100 110 120
 ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC
 130 140 150 160 170 180
 AACCCAGACCA CCTTATACCA GCGTTATGAG ATCAAGATGTA CCAAGATGTA TAAAGGGTTC
 190 200 210 220 230 240
 CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTG
 250 260 270 280 290 300
 TGC GGATACT TCCACAGGTC CCACAAACCGC AGCGAGGAGT TTCTCATTGC TGGAAAACTG
 C1
 C2
 310 320 330 340 350 360
 CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC
 370 380 390 400 410 420
 TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG
 430 440 450 460 470 480
 TTTCCCTGTT TATCCATCCC CTGCAAAC TG CAGAGTGGCA CTCATTGCTT GTGGACGGAC
 490 500 510 520 530 540
 CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCTG CCTGCCTCGG
 550 560 570 580 590 600
 GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA
 610 620 630 640 650 660
 GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTT CTTCCGGACA
 670 680 690 700
 ATGAAATAAA GAGTTACAC CCAGCAAAAA AAAAAAAGGAA TTC--

Please replace the paragraph [018], with the following paragraph:

C2
 --[018] A second preferred DNA sequence has been discovered which has an additional nucleotide sequence 5' to the initiator sequence. This sequence, which contains as the eighty-second through four-hundred-thirty-second nucleotides nucleotides 1 through 351 of the first preferred sequence set forth above, has the following nucleotide sequence (SEQ ID No: 6):

10 20 30 40 50 60
 GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT

70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG
430
GCTCCCTGGA AC--

C2
cont

Please replace the paragraph [019], with the following paragraph:

--[019] A third preferred DNA sequence which incorporates the 5' region of the second preferred sequence and the 3' sequence of the first preferred sequence, has the following nucleotide sequence (SEQ ID No: 7):

10 20 30 40 50 60
GGCCATCGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTT
70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG

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430 440 450 460 470 480
 GCTCCCTGGA ACAGCCTGAG CTTAGCTCAG CGCCGGGGCT TCACCAAGAC CTACACTGTT
 490 500 510 520 530 540
 GGCTGTGAGG AATGCACAGT GTTTCCCTGT TTATCCATCC CCTGCAAACACT GCAGAGTGGC
 550 560 570 580 590 600
 ACTCATTGCT TGTGGACGGA CCAGCTCCTC CAAGGCTCTG AAAAGGGCTT CCAGTCCCGT
 610 620 630 640 650 660
 CACCTTGCCT GCCTGCCTCG GGAGCCAGGG CTGTGCACCT GGCAGTCCCT GCGGTCCCAG
 670 680 690 700 710 720
 ATAGCCTGAA TCCTGCCCGG AGTGGAAAGCT GAAGCCTGCA CAGTGTCCAC CCTGTTCCCA
 730 740 750 760 770 780
 CTCCCATCTT TCTTCGGAC AATGAAATAA AGAGTTACCA CCCAGCAAAA AAAAAAAGGA--

C3
cont

Please replace the paragraph [030] with the following paragraph:

--[030] A first preferred portable DNA sequence of the present invention has a nucleotide sequence SEQ ID No: 5 as follows:

10 20 30 40 50 60
 GTTGTGCTG TGGCTGATAG CCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG
 70 80 90 100 110 120
 ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC
 130 140 150 160 170 180
 AACCAGACCA CCTTATACCA GCGTTATGAG ATCAAGATGA CCAAGATGTA TAAAGGGTTC
 190 200 210 220 230 240
 CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTC
 250 260 270 280 290 300
 TGCGGATACT TCCACAGGTC CCACAACCGC AGCGAGGAGT TTCTCATTGC TGGAAAATG
 310 320 330 340 350 360
 CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC
 370 380 390 400 410 420
 TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTT GCTGTGAGGA ATGCACAGTG
 430 440 450 460 470 480
 TTTCCCTGTT TATCCATCCC CTGCAAACACT CAGAGTGGCA CTCATTGCTT GTGGACGGAC
 490 500 510 520 530 540
 CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCTG CCTGCCTCGG

C4

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550 560 570 580 590 600
 GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA
 610 620 630 640 650 660
 GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTT CTTCCGGACA
 670 680 690 700
 ATGAAATAAA GAGTTACAC CCAGCAAAAA AAAAAAGGAA TTC--

(C4 cont)
 Please insert after [030], the following new paragraph:

--[030A] The first preferred portable DNA sequence encodes a metalloproteinase inhibitor having, as a mature protein, the amino acid sequence SEQ ID No: 1 of Table 1 (using the three letter abbreviations for amino acids). The amino acid at position +1 is cysteine (Cys). The amino acid at position +184 is alanine (Ala). As seen in the other preferred portable DNA sequences described below, the DNA sequence encoding a metalloproteinase inhibitor may also encode leader sequences. *(CS)*
 The leader sequences may be designated by negative numbers beginning with -1.

TABLE 1

	+1	9
	Cys Thr Cys Val Pro Pro His Pro Gln	29
Thr Ala Phe Cys Asn Ser Asp Leu Val Ile Arg Ala Lys Phe Val Gly Thr Pro Glu Val	Asn Gln Thr Thr Leu Tyr Gln Arg Tyr Glu Ile Lys Met Thr Lys Met Tyr Lys Gly Phe	49
Gln Ala Leu Gly Asp Ala Ala Asp Ile Arg Phe Val Tyr Thr Pro Ala Met Glu Ser Val	Cys Gly Tyr Phe His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu	69
Cys Gly Tyr Phe His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu	Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp Asn Ser Leu Ser	89
Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp Asn Ser Leu Ser	Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr Val Gly Cys Glu Glu Cys Thr Val	109
Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr Val Gly Cys Glu Glu Cys Thr Val	Phe Pro Cys Leu Ser Ile Pro Cys Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp	129
Phe Pro Cys Leu Ser Ile Pro Cys Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp	Gln Leu Leu Gln Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg	149
Gln Leu Leu Gln Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg	Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala	169
Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala	+184 SEQ ID NO: 1--	

Please replace paragraph [031], with the following paragraph:

(C6)
 --[031] A second preferred portable DNA sequence of the present invention has the following nucleotide sequence (SEQ ID No: 6):

10 20 30 40 50 60
GGCCATGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT
70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG
430
GCTCCCTGGGA AC--

Please replace paragraph [033], with the following paragraph:

--[033] A third preferred portable DNA sequence has the nucleotide sequence
(SEQ ID No: 7):

10 20 30 40 50 60
GGCCATGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTTT
70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAAAGT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAACT GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCGTG

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430 440 450 460 470 480
GCTCCCTGGA ACAGCCTGAG CTTAGCTCAG CGCCGGGGCT TCACCAAGAC CTACACTGTT
490 500 510 520 530 540
GGCTGTGAGG AATGCACAGT GTTCCCTGT TTATCCATCC CCTGCAAACCT GCAGAGTGGC
550 560 570 580 590 600
ACTCATTGCT TGTGGACGGA CCAGCTCCTC CAAGGCTCTG AAAAGGGCTT CCAGTCCCGT
610 620 630 640 650 660
CACCTTGCCT GCCTGCCTCG GGAGCCAGGG CTGTGCACCT GGCAGTCCCT GCGGTCCCAG
670 680 690 700 710 720
ATAGCCTGAA TCCTGCCCGG AGTGGAAAGCT GAAGCCTGCA CAGTGTCCAC CCTGTTCCCA
730 740 750 760 770 780
CTCCCATCTT TCTTCCGGAC AATGAAATAA AGAGTTACCA CCCAGCAAAA AAAAAAAGGA--

C7
Cont

Please paragraph [059], with the paragraph:

--[059] It is anticipated that translation of mRNA coding for the metalloproteinase inhibitor in yeast will be more efficient with the preferred codon usage of yeast than with the sequence present in pUC8-Fic, as identified in Example 2, which has been tailored to the prokaryotic bias. For this reason, the portion of the 5' end of the portable DNA sequence beginning at the *Tth111I* site is preferably resynthesized. The new sequence favors the codons most frequently used in yeast. This new sequence preferably has the following nucleotide sequence:

HgiAI
(SEQ ID No: 8) 5' GAT CCG TGC ACT TGT GTT CCA CCA CAC
(SEQ ID No: 9) GC ACG TGA ACA CAA GGT GGT GTG
CCA CAA ACT GCT TTC TGT AAC TCT GAC C
GGT GTT TGA CGA AAG ACA TTG AGA CTG GA 3'--

Please replace paragraph [075], with the following paragraph:

--[075] In this method, the portable DNA sequences are those synthetic or naturally-occurring polynucleotides described above. In a preferred embodiment of the

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present method, the portable DNA sequence has the nucleotide sequence SEQ ID No: 5 as follows:

10 20 30 40 50 60
GTTGTTGCTG TGGCTGATAG CCCCCAGCAGG GCCTGCACCT GTGTCCCACC CCACCCACAG

70 80 90 100 110 120
ACGGCCTTCT GCAATTCCGA CCTCGTCATC AGGGCCAAGT TCGTGGGGAC ACCAGAAGTC

130 140 150 160 170 180
AACCAGACCA CCTTATACCA GCGTTATGAG ATCAAGATGA CCAAGATGTA TAAAGGGTTC

190 200 210 220 230 240
CAAGCCTTAG GGGATGCCGC TGACATCCGG TTCGTCTACA CCCCCGCCAT GGAGAGTGTC

250 260 270 280 290 300
TGCGGATACT TCCACAGGTC CCACAAACCGC AGCGAGGAGT TTCTCATTGC TGGAAAAC TG

310 320 330 340 350 360
CAGGATGGAC TCTTGCACAT CACTACCTGC AGTTTCGTGG CTCCCTGGAA CAGCCTGAGC

370 380 390 400 410 420
TTAGCTCAGC GCCGGGGCTT CACCAAGACC TACACTGTTG GCTGTGAGGA ATGCACAGTG

430 440 450 460 470 480
TTTCCCTGTT TATCCATCCC CTGCAAAC TG CAGAGTGGCA CTCATTGCTT GTGGACGGAC

490 500 510 520 530 540
CAGCTCCTCC AAGGCTCTGA AAAGGGCTTC CAGTCCCGTC ACCTTGCCTG CCTGCCTCGG

550 560 570 580 590 600
GAGCCAGGGC TGTGCACCTG GCAGTCCCTG CGGTCCCAGA TAGCCTGAAT CCTGCCCGGA

610 620 630 640 650 660
GTGGAAGCTG AAGCCTGCAC AGTGTCCACC CTGTTCCCAC TCCCATCTTT CTTCCGGACA

670 680 690 700
ATGAAATAAA GAGTTACCAC CCAGCAAAAA AAAAAAGGAA TTC--

Please replace paragraph [084], with the following paragraph:

--[084] In certain circumstances, the metalloproteinase inhibitor will assume its proper, active structure upon expression in the host microorganism and transport of the protein through the cell wall or membrane into the periplasmic space. This will generally occur if DNA coding for an appropriate leader sequence has been linked to the DNA

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coding for the recombinant protein. The preferred metalloproteinase inhibitors of the present invention will assume their mature, active form upon translocation out of the inner cell membrane. The structures of numerous signal peptides have been published, for example by Marion E.E. Watson in Nuc. Acid Res. 12: 5145-5164, 1984, specifically incorporated herein by reference. It is intended that these leader sequences, together with portable DNA, will direct intracellular production of a fusion protein which will be transported through the cell membrane and will have the leader sequence portion cleaved upon release from the cell.--

C16
cont

Please replace paragraph [0104], with the following paragraph:

--[0104] The structure of FIBAC A is

(SEQ ID No: 10) GA TCC GCG ATC GGA GTG TAA GAA ATG TGC ACT
(SEQ ID No: 11) G CGC TAG CCT CAC ATT CTT TAC ACG TGA

TGC GTT CCG CCG CAT CCG CAG ACT GCT TTC
ACG CAA GGC GGC GTA GGC GTC TGA CGA AAG

TGC AAC TCT GAC C
ACG TTG AGA CTG GA--

C11

Please replace paragraph [0106], with the following paragraph:

C12

--[0106] Component oligonucleotide FA1 (SEQ ID No: 12) is:
GATCC GCGAT CGGAG TGTAA GAAAT GTGCA CTTGC--

C13

Please replace paragraph [0107], with the following paragraph:

--[0107] Component oligonucleotide FA2 (SEQ ID No: 13) is:
GGAACG CAAGT GCACA TTTCT TACAC TCCGA TCGCG--

C14

Please replace paragraph [0108], with the following paragraph:

--[0108] Component oligonucleotide FA3 (SEQ ID No: 14) is:
GTTC CGCCG CATCC GCAGA CTGCT TTCTG CAACT CTGAC C--

Please replace paragraph [0109], with the following paragraph:

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C15

--[0109] Component oligonucleotide FA4 (SEQ ID No: 15) is:
AGGTC AGAGT TGCAG AAAGC AGTCT GCGGA TGCGG C--

Please replace paragraph [0112], with the following paragraph:

C16

--[0112] Linker A1 (SEQ ID No: 16) is: AATTGGCAG--

Please replace paragraph [0113], with the following paragraph:

C17

--[0113] Linker A2 (SEQ ID No: 17) is: TCGACTGCC--

Please replace paragraph [0116], with the following paragraph:

--[0116] The sequence of the sense strand (SEQ ID No: 18) is:

10	20	30	40	50	60					
GAATT	TC	TGATA	GATATT	CATG	ACGTATT	TTG	GATGATA	AACG	AGGCG	CAAAA
E	T	E			F		M	H		
C	A	C			O		N	H		
O	Q	O			K		L	A		
1	1	5			1		1	1		

C18

70	80	90	100	110	
AATGAAAAAAG	ACAGCTATCG	CGATCGCAGT	GGCACTGGCT	GGTTTCGCTA	CCGTA
A	NF	PS			
L	RN	VA			
U	UU	UU			
1	12	1A			

120	130				
GCGCA	GGCCTCTGGT	AAAAGCTT			
H	S	H	M		HA
H	T	A	N		IL
A	U	E	L		NU
1	1	3	1		31--

Please replace paragraph [0120], with the following paragraph:

C19

--[0120] Linker B1 (SEQ ID No: 19) is: GATCCCAGGCCTGCA--

Please replace paragraph [0121], with the following paragraph::

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C20

--[0121] Linker B2 (SEQ ID No: 20) is: GGCCTGG--

Please replace paragraph [0136], with the following paragraph:

C21

--[0136] The second preferred sequence (SEQ ID No: 6) as set forth herein, i.e.,

10 20 30 40 50 60
GGCCATGCC GCAGATCCAG CGCCCAGAGA GACACCAGAG AACCCACCAT GGCCCCCTT
70 80 90 100 110 120
GACCCCTGGC TTCTGCATCC TGTTGTTGCT GTGGCTGATA GCCCCAGCAG GGCCTGCACC
130 140 150 160 170 180
TGTGTCCCAC CCCACCCACA GACGGCCTTC TGCAATTCCG ACCTCGTCAT CAGGGCCAAG
190 200 210 220 230 240
TTCGTGGGGA CACCAGAACT CAACCAGACC ACCTTATACC AGCGTTATGA GATCAAGATG
250 260 270 280 290 300
ACCAAGATGT ATAAAGGGTT CCAAGCCTTA GGGGATGCCG CTGACATCCG GTTCGTCTAC
310 320 330 340 350 360
ACCCCCGCCA TGGAGAGTGT CTGCGGATAC TTCCACAGGT CCCACAACCG CAGCGAGGAG
370 380 390 400 410 420
TTTCTCATTG CTGGAAAATC GCAGGATGGA CTCTTGCACA TCACTACCTG CAGTTCTGT
430
GCTCCCTGGA AC--

IN THE CLAIMS:

Please cancel claim 26 without prejudice or disclaimer. Please amend claim 25, as follows:

25. (Amended) A purified collagenase inhibitor protein, said protein consisting essentially of an amino acid sequence selected from among the following:

- a) amino acid sequence SEQ ID NO: 2; or
- b) the amino acid sequence of a) or of SEQ ID NO: 1, further having a Met at position -1; or
- c) the amino acid sequence of a) or of SEQ ID NO: 1, further having a leader sequence at the N-terminal, -1 position, wherein said leader sequence consists essentially of the following amino acid sequence from positions -38 to -1:

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